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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
|-----------------|-------------|----------------------|---------------------|------------------|

10/667,126

09/19/2003

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AMBI:086US

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EXAMINER

KIM, TAEYOON

ART UNIT

PAPER NUMBER

1651

MAIL DATE

DELIVERY MODE

03/10/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                                      |   |  |
|------------------------------|--------------------------------------|---|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/667,126 | <b>Applicant(s)</b><br>CONRAD, RICHARD C. |  |
|                              | <b>Examiner</b><br>TAEYOON KIM       | <b>Art Unit</b><br>1651                   |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 21 December 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-17, 19-48, 50 and 53-72 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-17, 19-48, 50 and 53-72 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Claims 1-17, 19-48, 50 and 53-72 are pending.

#### ***Response to Amendment***

Applicant's amendment and response filed on 12/21/2007 has been received and entered into the case.

Claims 18, 49, 51 and 53 have been canceled, and claims 1-17, 19-48, 50 and 53-72 are pending and have been considered on the merits. All arguments have been fully considered.

The objections to the specification and the claims 11-13 have been withdrawn due to the amendment.

The claim rejections under 35 U.S.C. §112 have been withdrawn due to the amendment except the claim rejection under 35 U.S.C. §112, 1<sup>st</sup> para., to claims 4 and 5 (see below).

In the response to the previous office action, applicant argued that Stratagene manual does not contemplate isolation of small RNA molecules less than 400 bases. Applicant asserted that Bost et al. or Ekenberg et al. do not teach isolation of small RNA molecules and thus the method of the combined references do not achieve isolation of small RNA molecules. This argument is not persuasive because although Stratagene manual does not particularly teach that the intended use of the method for small RNAs, it would have been inherently carried out by the method of Stratagene manual. It is well known in the art that the centrifugation step after alcohol precipitation of nucleic acids (RNAs) as taught by the manual would be less effective in recovery of such small RNAs

because of loss of such small molecules as a pellet formed after centrifugation step. However, this does not mean that the method of Stratagene manual cannot isolate small RNA molecules. The use of a glass support of Bost et al. in the method of the Stratagene manual, or any method of isolating nucleic acids, would enhance the yield of nucleic acids including small RNAs because it is expected that the use of solid support would result in a better recovery of small RNA molecules than the centrifugation step of Stratagene manual. This is further supported by Padhye et al. (US 5,808,041). Padhye et al. teach the use of silica gel and glass particles in purification of RNAs of virtually any length that occur naturally in cells, viruses or the like (see abstract and col. 6, lines 43-48). Therefore, the method of Stratagene manual in combination with the use of solid support such as glass silica of Bost et al. is capable of isolating small RNAs.

The citation of the size range of 400-2000 bases for most mRNA from the Stratagene manual does not necessarily suggest that the manual is only capable of isolating the RNAs within the given size range. The citation is a general statement that mRNAs are in the range of 400-2000 bases.

It is also reminded that the current claims do not particularly claim that the method steps are exclusively for small RNAs, and it appears that the method steps of the instant application would isolate RNAs with bigger sizes. The method of combined references is considered to be capable of isolating RNAs with a variety of sizes, including small RNAs, therefore, the references render the current claims obvious.

Applicant also asserted that the combination of Palmieri et al. in view of Ekenberg et al. lacks a teaching or suggestion of the presently claimed invention. It

appears that applicant mistakenly refers Palmieri et al. It is understood that it is meant to be Bost et al. This argument is not persuasive because a person of ordinary skill in the art recognizes the use of a solid support of Bost et al. is well known in the art for isolating nucleic acids, and since the use of such support is considered to be a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. Therefore, it would have been obvious to a person of ordinary skill in the art to try the solid support of Bost et al. in the method of purifying nucleic acid of Stratagene manual.

The Supreme Court recently states in *KSR v. Teleflex* (550 US82 USPQ2d 1385, 2007) "The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." *Id.*, at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

Furthermore, the combination of the teaching by Ekenberg et al. with Stratagene manual and Bost et al. is considered to be art-recognized alternative to the centrifugation step of the manual to remove solution from the mixture and collect the beads (solid supports).

M.P.E.P. §2144.07 states “The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) (Claims to a printing ink comprising a solvent having the vapor pressure characteristics of butyl carbitol so that the ink would not dry at room temperature but would dry quickly upon heating were held invalid over a reference teaching a printing ink made with a different solvent that was nonvolatile at room temperature but highly volatile when heated in view of an article which taught the desired boiling point and vapor pressure characteristics of a solvent for printing inks and a catalog teaching the boiling point and vapor pressure characteristics of butyl carbitol. “Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle.” 325 U.S. at 335, 65 USPQ at 301.)”.

Therefore, the combination of Bost et al. and Ekenberg et al. with Stratagene manual does not require teaching-suggestion-motivation test as asserted by applicant.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 5 disclose the phrase “using 4 volumes of ethanol”. It is not clear what subject matter to be compared to for the term “4 volumes”.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 4 and 5 disclose a yield of the purification step being at least about 20% or 50%. It is not clear how the percentage of yield can be obtained without knowing the starting amount of small RNAs present in the cells. However, the specification does not disclose how a person of ordinary skill in the art to determine the total small RNAs present in cells. Without knowing how to determine the total amount of small RNAs present in any cell utilized in the method of current invention, a person of ordinary skill in the art would not have obtained the yield of small RNAs obtainable from the method of the current invention.

The newly added limitation does not overcome the written description requirement. The new limitation provides a comparison point but does not provide the amount of starting materials for the calculation of percentage yield.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-17, 19-48, 50 and 53-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over a manual for micro RNA isolation kit (Stratagene, 2000) in view of Bost et al. (US 6,111,096) in further view of Ekenberg et al. (US 6,218,531).

Claims 1-17, 19-48, 50 and 53-72 are drawn to a method of purifying small RNA (microRNA) comprising steps of lysis of cells using a lysing solution comprising a detergent or a chaotropic agent, precipitation of RNA with alcohol (ethanol), precipitation of proteins with guanidinium and/or phenol and chloroform, applying the lysate to a solid support, eluting small RNA from the support with low-ionic strength solution, collecting the eluted small RNA; a method for isolating miRNA or siRNA from cell lysates comprising a) obtaining a sample having miRNA or siRNA, b) adding an alcohol solution at about 35 to 70% to the sample, c) adding an extraction solution to the sample, d) applying the sample to a mineral or polymer support, and e) eluting the siRNA or miRNA from the support; a limitation to the eluted miRNA or siRNA being enriched at least about 10-fold by mass; a method of isolation small RNA comprising steps of lysing cells, adding alcohol to the lysate, applying the lysate/alcohol mixture to a first solid support, collecting flow-through and adding alcohol to the flow-through and then applying to a second solid support, and eluting small RNA, wherein the alcohol concentration of the mixture applied to the first support being about 20% to 35% alcohol, wherein the alcohol concentration of the mixture applied to the second support being about 35% to 70% alcohol.



Stratagene manual teaches a method comprising steps of lysis of cells (see p.7) using a denaturing solution which contains 4 M guanidine isothiocyanate (guanidinium), 0.5% sarcosyl (N-lauroyl sarcosine) and 20 mM sodium acetate (buffer) (see p.21), extraction with phenol and chloroform (see p.8), adding isopropanol (alcohol) to the lysate.

Stratagene manual does not teach the use of solid support such as glass or silica material or eluting small RNA from the solid support.

Bost et al. teach the solid phase (solid support) such as glass or silica material in a form of bead (see paragraphs [0060] and [0065]) for RNA isolation, first wash solution containing chaotropic agent, guanidine thiocyanate (see Example 5), wash solution containing ethanol (see paragraph [0100], Example 5), and a step for eluting nucleic acids from the solid support with a low ionic strength solution containing 10 mM Tris at 56°C (see paragraph [0118], Example 5).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to try to use the solid support and washing steps of Bost et al. in the method of Stratagene manual because both methods are drawn to isolation of RNA, and the use of solid support in purification of nucleic acid is well known in the art, which provides convenience and higher purity in purification of nucleic acids.

The Supreme Court recently states in *KSR v. Teleflex* (550 US82 USPQ2d 1385, 2007) “The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was “obvious to try.” *Id.*, at 289 (internal quotation marks omitted). When there

is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.”

Claim 20 discloses the step of adding alcohol in the lysate prior to extraction with an organic solvent. It would have been obvious for a person of ordinary skill in the art at the time of invention made to switch the order of steps.

M.P.E.P. § 2144 recites, “The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law...If the facts in a prior legal decision are sufficiently similar to those in an application under examination, the examiner may use the rationale used by the court.” In *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946), the court found that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. In *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930), the court found that selection of any order of mixing ingredients is *prima facie* obvious.

Although Stratagene manual in view of Bost et al. do not particularly teach the washing solution containing guanidinium and alcohol (claims 23 and 60), it would have

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been obvious to a person of ordinary skill in the art to add guanidinium in the washing solution because it is well known in the art that guanidinium is added to inactivate RNase, which degrades RNA molecules, and protect RNAs from degradation. Thus, the addition of guanidinium in the washing solution would be considered to be beneficial to protect RNA molecules from degradation.

With regards to the limitation disclosed in claims 24 and 61, it would have been obvious to a person of ordinary skill in the art to have additional washing step to enhance the removal of unwanted materials bound to the silica material. Furthermore, Bost et al. teach multiple washing steps in isolating RNAs (see Example 5).

The limitation of claim 26 of eluting small RNA from the solid support at about 60°C to about 100°C is obvious over the disclosure of Stratagene manual (see p.5) as well as Bost et al. Bost et al. disclose a step of eluting nucleic acid with an elution buffer at 56°C. The manual teaches application of heat at 68°C to enhance solubilization of RNA. Therefore, a person of ordinary skill in the art would have recognized that higher temperature would enhance elution of nucleic acids (small RNA) bound to the solid support and applied heat at 68°C to enhance elution of small RNA from the solid support as taught by Stratagene manual in view of Bost et al.

Bost et al. teach the step of using centrifugation (see paragraph [0118]) to collect the set of beads as disclosed in claim 31.

Although Stratagene in view of Bost et al. do not teach filtration or magnetic capture for the collection of the set of beads, Ekenberg et al. teach filtration using vacuum to collect silica support (see column 6, lines 16-17) and as an alternative to

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centrifugation. Furthermore, Ekenberg et al. teach silica matrix in the form of magnetic beads, indicating a capability of magnetic capturing of the beads (see column 5, lines 38-41). Thus, it would have been obvious to a person of ordinary skill in the art to substitute centrifugation with filtration or magnetic capture, since it is well known in the art that filtration or magnetic capturing is an alternative way to substitute centrifugation to collect beads.

Although Stratagene in view of Bost et al. do not particularly teach the use of glass fiber as a solid support, it is well known in the art that glass fiber is an art-recognized equivalent of silica material as taught by Ekenberg et al. (see column 4, lines 13-17). Thus, it would have been obvious to a person of ordinary skill in the art to substitute silica gel or matrix of Bost et al. with glass fiber of Ekenberg et al.

Although Stratagene in view of Bost et al. in further view of Ekenberg et al. are silent in isolating small RNA such as miRNA or siRNA, since the method of the references is similar, if not identical, to the claimed invention in isolation of RNAs, and it is expected that the purified RNAs would encompass small RNAs with less than 200 nucleotides. Furthermore, Bost et al. teach that the method of Bost et al. utilizing solid support would be able to isolate tRNA or fragmented nucleic acid, which is a disclosed species of small RNAs in the instant application (see paragraph [0059]). Therefore, the initial method steps of Stratagene which is for isolation of total RNAs from the cells or tissues, including small RNAs, would be further purified by the use of a solid support of Bost et al., allowing isolation of small RNAs such as tRNAs. Therefore, the intended use of isolating small RNA of the claimed invention would be carried out by the method of

Stratagene in view of Bost et al. in further view of Ekenberg et al. unless proven otherwise.

With regard to the limitation to the concentration of guanidine isocyanate (chaotropic salt) (i.e. 1.6 M) in claim 72, Ekenberg et al. teach the concentration of chaotropic salt being between about 1 M and 6 M, and the preferable chaotropic salt being guanidine thiocyanate (which is sometimes referred to as guanidine isocyanate) (see column 14, lines 17-20).

Although Stratagene in view of Bost et al. in further view of Ekenberg et al. do not particularly teach each and every specific concentration of alcohol (e.g. 35-70% in a lysate/alcohol mixture; or 80% ethanol in wash solution) or the fold enrichment (i.e. 10-fold) of miRNA or siRNA, it would have been obvious to a person of ordinary skill in the art to optimize the concentration of alcohol or fold enrichment because a person of ordinary skill in the art would have recognized those concentration as result-effective variables. As such, the variables would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by those references. Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the

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claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); \*\* In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made especially in the absence of evidence to the contrary.

With regard to the method steps (e) through (g) disclosed in claim 50, which requires applying the flow-through lysate/alcohol mixture collected from step (d), it would have been obvious to a person of ordinary skill in the art to repeat the steps of applying flow-through from the first solid support by applying the flow-through to the second solid support not to loose unbound nucleic acids from the first reaction between the lysate and a solid support.

Therefore, the invention as a whole would have been prima facie obvious to a

person of ordinary skill at the time the invention was made.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAEYOON KIM whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 4:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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/Leon B Lankford Jr/  
Primary Examiner, Art Unit 1651

Taeyoon Kim  
AU-1651